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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/501,643	02/10/2000	Dr. Larry Sklar	UNME-0070-1	4170

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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	16

DATE MAILED: 08/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/501,643	SKLAR ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-27,46 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-27 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/13/02 has been entered.

Amendment Entry

2. Applicant's amendment and response filed 5/13/02, in Paper No. 15 is acknowledged and has been entered. Claims 8 and 28-45 have been cancelled. Claims 1-2 and 9-14 have been amended. Claims 46-47 have been added. Accordingly, claims 1-7, 9-27, and 46-47 are currently pending and are under examination.

Rejections Withdrawn

3. The rejections of claims 8 under 35 U.S.C. 102 and 103 are now moot in light of Applicant's cancellation of the claim.

4. In light of Applicant's argument, the rejection of claims 1-3, 9-12, 15-19, and 26-27 under 35 U.S.C. 103(a) as being unpatentable over Parce et al. (US 6,150,180) in view of Hach et al. or Trinel et al. (US 4,116,631), is hereby, withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 9-10, 26, and 46-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is indefinite in lacking antecedent support for the recitation of "said tube".

Claim 26 is confusing in relation to claim 1 from which it depends in reciting, "(means for) injecting a buffer between adjacent samples ..." because in claim 1, the separation gas appears to perform separation function between adjacent samples. Please clarify.

The term "or less" in claims 46-47 is a relative term which renders the claim indefinite. The term "or less" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-3, 5, 7, 9-12, 15-19, and 26-27 stands rejected under 35 U.S.C. 102(b) as being anticipated by Saros et al. (US 4,853,336) for reason of record.

Saros et al. disclose a single tubing (channel/conduit) continuous flow analyzer system in which a successive plurality of samples (liquid segments) containing biomaterial and test compounds (analysis mixtures) are separated by immiscible segments which permit delayed on-line mixing of the components in the mixtures in the single conduit (see Abstract, column 2, lines 40-55, column 4, lines 8-26 and Figure 4). Saros et al. specifically disclose a flow system comprising an autosampler for moving a plurality of samples, a means for introducing a separation gas (immiscible intervening segment) between each sample, and the tubing for passage of fluid stream therethrough. The walls of the tubing have an expanded diameter sufficient to render the separation gas, non-occluding (see column 3). The autosampler includes a probe which aspirates the samples, test compounds, reagents (buffer fluid), and the separation gas. The autosampler is connected to a bidirectional linear drive means (see column 5, lines 1-10). Saros et al. disclose that the probe is coated with immiscible liquid. The movement or aspiration of the samples is effected by a peristaltic pump which is located downstream of the system tubing (see column 5, lines 14-21 and

column 6, lines 52-55). Biomaterials in the samples are fluorescently tagged so that fluorescent signals associated with their function upon reaction with test compounds provide detectable events during analysis (see column 11, lines 23-36). In teaching that the probe and tubing in the flow system is coated with immiscible liquid, Saros et al. is, therefore, said to have inherently anticipated a hydrophobic probe or a probe coated with hydrophobic material.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 4, 6, 13-14, 20-24, and new claims 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saros et al. (US 4,853,336) in view of Kercso et a. (US 6,132,685) for reason of record.

Saros et al. has been discussed supra. Saros et al. differ from the claimed invention in failing to disclose the source well as a well plate comprising 96, 384, or 1536 source wells. Saros et al. further differ in failing to disclose that the flow tubing or channels are made of polyvinyl chloride (PVC).

Kercso et al. disclose high throughput microfluidic flow systems for analyzing a large number of sample compounds. The samples to be analyzed are contained in standard multiwell microtiter plates such as those having 96, 384,1536, or higher numbers of wells and are transferred sequentially from the wells into a tubing or channel system. These multiwell plates travel along a conveyor system between an input stack and an output stack, and are sequentially aligned in the input port for autosampling by a tubular autosampler (pipettor) which extends below affixed to the microfluidic channel substrate (see column 3 and 11). These microfluidic flow channels are fabricated on the planar substrate comprising polymeric materials which are inherently hydrophobic such as polyvinylchloride (PVC) and polyurethane.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the sample source taught by Saros with the microtiter plates taught by Kercso because Saros specifically taught sequentially analyzing a successive numbers of samples which are separated by immiscible segments in order to effect analysis of a plurality of samples using the continuous flow analyzer system

and Kercso specifically taught the advantage of using multiwell plate sampling for handling and sequentially introducing even larger numbers of samples to effect analysis thereto. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the multiwell plates of Kercso into the flow analyzer taught by Saros because Kercso specifically taught the added advantage of rapid and expedient analysis of large numbers of samples and test compounds in small volumes achieved by their sequential introduction from multiwell structures into automated flow analyzers and other microfluidic systems.

Saros et al. and Kercso et al. differ in failing to disclose that the flow tubing or channels made of PVC have an inner diameter of 0.01 to 0.03 inches and a wall thickness of 0.01 to 0.03 inches, such as recited in claim 13 or an inner diameter of 0.02 inches and a wall thickness of 0.02 inches, such as recited in claim 14. Further, Saros et al. and Kercso et al. fail to disclose that a portion of the fluid stream passing through the pump is contained within a tube having an internal diameter of 0.02 inches or less, such as recited in claim 46 and 47. Saros et al. and Kercso et al. also fail to disclose that the probe has a conical tip and the source wells on the microwell plates have conical shapes as well.

However, it is maintained that parameter requirements in flow systems or microfluidic channels such as inner diameter of 0.01 to 0.03 inches and wall thickness of 0.01 to 0.03 inches, or volumetric capacity of tube having an internal diameter of 0.02 inches or less ,or shape requirements of autosampling probe tips such as tubular or conical shapes/structures are all result effective variables which the prior art references

have shown may be altered in order to achieve optimum results. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum parameter of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitations recited in instant claims 13, 14, 4, 24, and 46-47 are for any particular purpose or solve any stated problem and the prior art teaches that flow analysis system requirements often vary according to the samples, types, and numbers thereof, being analyzed and various parameters taught by the prior art appear to work equally as well; absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable parameters and requirements of the methods disclosed by the prior art by normal optimization procedures.

8. Claims 25 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Saros et al. (US 4,853,336) in view of Kercso et a. (US 6,132,685) and in further view of Farrell et al. (US 5,788,927) for reason of record.

Saros et al. and Kercso et al. have been discussed supra. Saros et al. and Kercso et al. differ in failing to teach that the well plate is mounted in an inverted position.

Farrell et al. teach a flow analyzer system which incorporates an automated sample aspiration design into its hydraulic system wherein a sealed sample source is inverted and moved relative to the probe of the autosampler for autosampling. The probe tip or needle of the autosampler penetrates the seal of the sample source to aspirate the sample contained within (see column 7).

The inverted mounting design of the well plate as recited in claim 25 has been specifically suggested by Farrel et al. and constitute an obvious modification or design choice which is routinely varied in microfluidic or flow systems art and which has not been described as being critical to the practice of the invention.

Response to Arguments

9. Applicant's arguments filed 5/13/02 have been fully considered but they are not persuasive.

A) Applicant argues that Saros fails to teach or suggest a flow cytometer such as recited in the claimed invention wherein the flow cytometer has two fluid phases, a narrow hydrodynamically focused core sample stream that carries particles and an outer sheath stream of much larger volume. According to Applicant, large air bubbles cause sustained disturbance of the hydrodynamic focusing, resulting in misalignment of the sample through the laser beam. Therefore, the presence of air is disruptive in the

alignment in the flow stream of a flow cytometer, and therefore, it is not obvious to use an air bubble as a sample separator in flow cytometers. Applicant argues that flow cytometers teach against use of air bubbles and encourages removing any air bubbles prior to passing the fluid through the flow cytometers.

Contrary to Applicant's argument, claim 1, as recited, reads on the teaching of the flow analyzer taught by Saros. Claim 1 recites a flow cytometer, that detects particles from a plurality of samples, comprising: a) a means of moving the samples from source wells into a fluid flow stream comprising a pump, b) means for introducing a separation gas between samples, and c) cytometric detector, for selective analysis of the particles through the flow cytometer. Saros discloses a single tubing (channel/conduit) wherein a successive plurality of samples containing biomaterial and test compounds are moved and separated by gas, an autosampler, and a means for introducing a separation gas between each sample. Saros discloses a peristaltic pump to aspirate and move samples. Saros discloses a detector to analyze detectable events from biomaterials which are fluorescently tagged, so that fluorescent signals associated with their function upon reaction with test compounds are detected. See discussion supra.

Applicant's claim 1 recites and defines means plus functions of an apparatus which are fully described and defined in the apparatus taught by Saros. As such, no patentable distinction is seen.

In response to applicant's argument that Saros fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a flow

cytometer which has two fluid phases, a narrow hydrodynamically focused core sample stream that carries particles and an outer sheath stream of much larger volume, because of the requirement of hydrodynamic focusing to maintain steady stream) are not recited or reflected in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Further, a recitation of the intended use of the claimed apparatus must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

B) Applicant argues that it is not obvious to use air bubbles as a sample separator in a flow cytometer, as known in the art. In flow cytometric art, it is desirable to remove bubbles but Applicant discovered that by controlling the size of the air bubbles, disruption of hydrodynamic focusing can be prevented; thus allowing the known flow cytometer to be used with a flow stream containing bubbles. Therefore, the combination of the teaching of Saros with that of Kercso, does not render obvious the teaching of the claimed invention.

In response and as discussed supra, Applicant's claim 1 recites and defines means plus functions of an apparatus which are fully described and defined in the

apparatus taught by Saros and further rendered obvious by Kercso. As such, no patentable distinction is seen.

In response to applicant's argument that the teaching of Saros in combination with Kercso does not render obvious the teaching of a flow cytometer, having two fluid phases, a narrow hydrodynamically focused core sample stream that carries particles and an outer sheath stream of much larger volume, because of the requirement of hydrodynamic focusing to maintain steady stream, it has been noted that such features are not distinctly recited or reflected in the rejected claims. Specifically, Applicant's claim 1 does not define or reflect the flow cytometer described in Applicant's arguments. It therefore follows, that the unexpected result obtained by Applicant from the known flow cytometer in the art, cannot be applied to the claimed apparatus since there is no hydrodynamic focusing involved, required, or otherwise inferred, in the claimed apparatus. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Further, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed apparatus and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

C) Applicant argues that claims 1-7 and 9-27 have been rejected on the basis of facts within the personal knowledge of the Examiner.

In response, claims 1-7 and 9-27 have been rejected on the basis of the recited flow cytometer apparatus and defined in claim 1 by Applicant, in comparison to what is described and defined as a flow analyzer by Saros, the analysis of which is based on one with ordinary skill in flow cytometric art. As discussed in A) and B) supra, Applicant's recited claims of a flow cytometric apparatus read on the teaching of Saros and are further rendered obvious by the combination of Saros and Kercso. As recited, no patentable distinction is seen.

10. For reasons aforementioned, no claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday-Thursday from 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
Patent Examiner
Art Unit 1641

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